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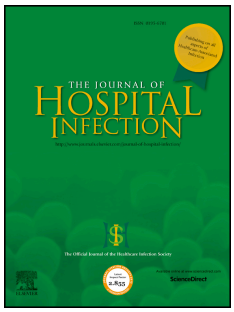

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The effect of using Fidaxomicin on recurrent *Clostridium difficile* infection?

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ABSTRACT

Fidaxomicin is a macrocyclic antibiotic licensed for treating *Clostridium difficile* infection (CDI). In the UK, fidaxomicin is often reserved for severe CDI or recurrences. At Queen Elizabeth Hospital Birmingham, all courses of fidaxomicin during 2017/18 were reviewed. Thirty-eight patients received fidaxomicin, of which 64% patients responded to treatment when fidaxomicin was given during the first episode of a mild CDI. Conversely, all patients with recurrent CDI (rCDI) failed treatment with fidaxomicin. There were mixed results with using fidaxomicin for severe CDI, with only 42% of patients responding. Our results suggest fidaxomicin is best suited as a treatment for mild CDI during a patient's first episode.

INTRODUCTION

Clostridium difficile infection (CDI) causes a range of symptoms from mild diarrhoea to life threatening pseudomembranous colitis.[1-4] The majority of patients experience a single episode of infection, however, despite treatment, some develop further episodes termed rCDI.[1] It is estimated that, following initial resolution of symptoms, rCDI occurs in 20%–30% of patients. Fidaxomicin is a macrocyclic antibiotic licensed for treating CDI. Fidaxomicin has been shown to have comparable clinical cure when compared to vancomycin.[1-2] In the UK, vancomycin and fidaxomicin are generally reserved for severe CDI or for subsequent recurrences.[5] There are limited data on fidaxomicin and its effect/usefulness in the treatment of rCDI and severe CDI.[5] Recently, Enoch *et al* reviewed all episodes of fidaxomicin use at an English hospital in order to assess patient outcome data.[5] They described fidaxomicin use in 15 patients with rCDI, concluding that, although fidaxomicin was well tolerated, the utility of fidaxomicin at this stage of infection is unclear.[5] At QEHB, our treatment algorithm includes first line therapy with metronidazole for patients with mild to moderate CDI, vancomycin for relapsed or severe CDI, followed by fidaxomicin in the event of treatment failure or faecal microbiota transplant (FMT) after two recurrences/ treatment failures.[6] During 2017/18, 38 patients received fidaxomicin for CDI at QEHB. Similar to Enoch *et al* we reviewed all episodes of fidaxomicin prescription in order to assess patient outcome data.[5]

METHODS

Setting. Queen Elizabeth Hospital Birmingham (QEHB), part of University Hospitals Birmingham (UHB) NHS Foundation Trust is a tertiary referral teaching hospital in Birmingham, UK that provides clinical services to over one million patients every year.

C. difficile testing. In line with national guidance, an algorithmic approach to identifying CDI is undertaken at QEHB.[4,7-9] A three-stage algorithm is employed.[7-9] Briefly, any patient with ≥1 episode of unexplained diarrhoea has their faecal specimen tested for CDI. The CDI testing algorithm consists of an initial screening step using a Premier GDH EIA (Meridian Bioscience, Cincinnati, Ohio), followed by a NAAT (Cepheid, Xpert™ *C. difficile*, US) for GDH positive samples only.[7] All samples testing GDH and NAAT positive have a Premier Toxins A and B EIA (Meridian Bioscience, Cincinnati, Ohio).[7]

Study design and definitions. We carried out a single centre observational retrospective cohort study where all patients aged ≥18 years commenced on fidaxomicin during April 2017 to March 2018 were reviewed for clinical response to CDI treatment. All 38 patients who were positive by GDH and NAAT, and treated with fidaxomicin, between April 2017 to March 2018 were included in the study. We analysed the Bristol Stool Chart (BSC) and clinical features, based on the daily assessment infection severity tool (DAISY) as previously described.[6] The DAISY tool was also used to define mild, mild/moderate and severe forms of CDI.[6] In addition, we collected details of the outcome of the patients (at end of therapy and, at 30 and 90 days post-cessation of therapy: resolution of diarrhoea, ongoing diarrhoea or death). Time until diarrhoea resolution was defined as per Enoch *et al*.[5]

Recurrent CDI. Recurrent CDI was defined as the return of diarrhoea (≥1 episode of

unexplained diarrhoea) within 28 days of a previous CDI episode and the presence of a positive test result for toxigenic *C. difficile* by GDH and NAAT.[6-7]

Treatment failure. Was defined as cases where failure to respond to treatment resulted in a change of CDI therapy of the patient.[9-10]

Clinical data collection. Patient data collected at the time of a positive result included: patient demographics (age, sex), markers of CDI severity (white cell count, C-reactive protein, serum creatinine, serum albumin, temperature, stool frequency) and mortality (one month and 3-month all-cause mortality).

RESULTS

Fidaxomicin treatment. During 2017/18, there were 356 toxin positive results occurring in 293 patients. Twenty one percent of these patients had more than one positive toxin result, including 10 patients who had 3 or more positive toxin results. All 38 patients treated with fidaxomicin received the recommended course of 200mg twice daily administered orally for 10 days. Treatment failure with fidaxomicin was declared after the recommended course and duration. Sixteen patients had mild to moderate CDI, 12 had severe CDI and 10 had rCDI (Table I); no patients received fidaxomicin as first line therapy. Whereas the response rates to fidaxomicin in patients with mild to moderate and severe CDI were 63% and 42%, respectively, no patient with rCDI responded. The recurrent CDI patients were prescribed fidaxomicin on average 4.3 months after their first CDI (fidaxomicin prescription ranging 1 to 10 months after the first CDI episode). Five of the rCDI patients had mild symptoms, 4 had mild/moderate CDI with 1 having severe CDI. Fidaxomicin was well tolerated with no adverse effects documented for any patient.

First episode of C. difficile. Twenty of the 38 patients received fidaxomicin during their first episode of CDI where symptoms did not resolve on first line treatment with metronidazole and/or vancomycin. Eleven of the patients received metronidazole as first line treatment, which was escalated to vancomycin. Eleven (55%) of these 20 patients responded to fidaxomicin (Table I). Time to resolution of symptoms ranged from 4-10 days (median 8 days). Patients with mild to moderate CDI were more likely to respond than patients with severe disease (64% versus 33%). Ten of the 11 patients who responded remained symptom-free at 90 days (the other patient died 60 days after completing therapy of reasons unrelated to CDI).

DISCUSSION

Overall, our work confirms the findings of Enoch *et al* that there was a poor outcome for patients with rCDI treated with fidaxomicin.[5] In our patient population, all patients with rCDI failed treatment with fidaxomicin, whereas Enoch *et al* reported a 50% failure rate.[5] Our results suggest fidaxomicin is best suited as a treatment for a mild CDI during a patients first episode rather than current UK guidance suggesting for use for severe or rCDI.[10] Likewise, a recent systematic review by Bienortas *et al* suggested that fidaxomicin frequently provides a sustained cure for non-multiple recurrent infections of CDI compared with vancomycin.[11] This is not surprising, as fidaxomicin may persist on *C. difficile* spores, whereas vancomycin does not.[12] This persistence could prevent subsequent growth and toxin production in vitro; having implications on spore viability, thereby impacting rCDI rates.[12] Current guidelines suggest that vancomycin and fidaxomicin are of equal efficacy for treating first recurrences of CDI.[10] They recommend oral vancomycin or fidaxomicin for second (or subsequent) recurrences of CDI, citing evidence from Cornely *et al* and Louie *et al* where success was seen using fidaxomicin to treat rCDI.[13-14] This is in contrast to our data, and those of Enoch *et al*.[5] Confounders cannot be ruled out as a reason for these discrepancies, and further work with larger numbers of patients is needed; however we note that none of the rCDI patients in our study were immunosuppressed. We have previously reported a lower rCDI rate (16%) than the national average of 25%, and suggested that this may be due to the novel ways of managing CDI on our hospital.[6] In particular, our use of a daily assessment of infection severity tool to monitor patients CDI progression and tailor CDI treatment accordingly may select for a particularly recalcitrant group of rCDI patients.[6]

In conclusion, our experience, and that of Enoch *et* al,[5] supports the use of faecal microbiota transplantation for the treatment of rCDI as per the recent joint British Society of Gastroenterology and Healthcare Infection Society guidance.[15] We have reported up to 90% success rate of treating rCDI with FMT.[7] With the cost of a 10-day course of fidaxomicin being around £1350, compared with £650 for FMT, we suggest that fidaxomicin should mainly be be considered as a treatment option for non-multiply recurrent CDI.

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Conflict of interest statement

None declared.

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Table I. Treatment outcomes at the end of 30 days with patients treated at QEHB with Fidaxomicin in 2017/18.

	All treatment				Treated within first episode			
	Responded	Failed	Total	Percentage	Responded	Failed	Total	Percentage
Mild	10	6	16	63	9	5	14	64
Severe	5	7	12	42	2	4	6	33
rCDI*	0	10	10	0	-	-	-	-
Total	15	23	38	39	11	9	20	55

NB. * of these 5 patients had mild CDI, 4 patients had mild/moderate CDI and 1 patient had severe CDI.